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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,090	BARON ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,58,60,61 and 69-74* is/are pending in the application.

4a) Of the above claim(s) *61,73 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,58,60 and 69-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *43,58,60,61 and 69-74* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 6/25/08 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 6/25/08 has been entered in full. Claims 43, 58, 60 and 61 are amended. Claim 1-42, 57, 59 and 62-68 are canceled (Claims 44-56 were previously canceled). New claims 69-74 are added.

Claims 43, 58, 60, 61 and 69-74 are pending.

In the Office Action mailed 9/20/07 Applicants were required to elect a single species of "enhanced vascular growth". Applicants' election of "enhanced vascular growth accompanying a solid tumor" in the reply filed on 10/22/07 is acknowledged.

Claim 61 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. It is noted that Applicants have indicated that the status of this claim is "Currently amended". However, the correct status identifier should be "Withdrawn—currently amended".

New claims 73 and 74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of enhanced vascular growth (hemangioma), there being no allowable generic or linking claim.

Claims 43, 58, 60 and 69-72 are under consideration, as they read upon the elected species.

Information Disclosure Statement

The Information Disclosure Statement of 6/25/08 has been considered.

Withdrawn Objections and/or Rejections

All rejections of claims 57, 59 and 62-68 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 43, 58 and 60 under 35 U.S.C. § 112, first paragraph at pg 7-10 of the 1/8/08 Office Action for failing to comply with the written description requirement is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 43 and 58 under 35 U.S.C. § 112, first paragraph at pg 10-12 of the 1/8/08 Office Action for containing new matter is *withdrawn* in view of Applicants' amendments to the claim.

At pg 2 of the 5/20/08 Advisory Action, it was set forth that the proposed amendments submitted after final would raise the issue of new matter. On further consideration, and in view of Applicants' persuasive arguments at pg 5-7 of the 6/25/08 response, this statement is now withdrawn. Claim 43 as originally filed on 2/3/04 stated, "A method of treating abnormally enhanced vascular growth in a subject comprising: (a) selecting an effective dose of a hedgehog compound capable of inhibiting the activity of a gene product expressed in an embryonic tissue; and (b) administering the compound to the subject over an effective time so as to inhibit abnormally enhanced vascular growth". The specification further teaches that "hedgehog proteins are expressed in extraembryonic tissue" (¶ 90 of the published application). The specification further teaches that hedgehog compounds include "antibodies specific for hedgehog protein epitope" (¶ 95). The specification further teaches that "methods are provided for inhibiting vascular growth in subjects suffering from excess vascularization or neovascularization as found in, for example, a variety of solid tumors such as breast cancer, hemangiomas in infancy, ocular neovascularization associated with diabetes, bleeding disorders of the female reproductive tract, and certain forms of arthritis" (¶ 118). The specification further demonstrates that a Shh blocking antibody inhibits the activity of Shh with regard to primitive erythropoiesis (Example 4). Thus, Applicants'

arguments that the specification as originally filed appreciates the Shh blocking antibody as an antagonist to be used in the claimed method is found to be persuasive.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43, 58, 60 and 69-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth previously and maintained at pg 3-7 of the 1/8/08 Office Action for claims 43, 58, 60; new claims 69-72 are herewith included.

For clarity, the rejection is first restated in view of Applicants' amendments to the claims and then Applicants' arguments are addressed.

Independent claims 43 and 70 encompass a method of inhibiting abnormally enhanced vascular growth in a subject, or of inhibiting vascular growth in a subject suffering from excess vascularization or neovascularization, comprising administering an amount of a Sonic hedgehog blocking antibody effective to inhibit abnormally enhanced vascular growth. Claim 58 limits the method to one that inhibits angiogenesis. The elected species of abnormally enhanced vascular growth under consideration is growth is a solid tumor; claims 60, 69, 71 and 72 are limited to said species. Claims 69 and 72 further limit the solid tumor to breast cancer.

The term "vascular" refers to vessels that circulate biological fluids such as blood or lymph; therefore "vascular growth; "vascularization"; and "neovascularization" includes vasculogenesis and angiogenesis of blood and lymph vessels. With respect to blood vessels the relevant art teaches, “[i]n vasculogenesis, endothelial cells are differentiated *de novo* from mesodermal precursors, whereas in angiogenesis, new

blood vessels are generated from pre-existing ones. Vasculogenesis occurs only during embryonic development and leads to formation of a primary capillary plexus. In angiogenesis, new capillaries form and remodel by budding (sprouting), splitting (intussusception) and fusion (intercalated growth), producing a juvenile vascular system and then a mature one" (pg 2013 of Cohen Jr, 2006. American Journal of Medical Genetics. 140A: 2013-2038; cited previously). However, other teachings in the relevant art suggest that vasculogenesis may also contribute to blood vessel formation in adult mammals; however, the role of this contribution is not well-characterized (see pg 157 of Ribatti et al. 2001. Mechanisms of Development. 100: 157-163; cited previously).

Claims 43, 58 and 70 are extremely broad with respect to the encompassed conditions related to vascular growth. Treatment of "abnormally enhanced vascular growth" includes abnormally enhanced vascular growth that occurs in either embryonic vascularization or adult angiogenesis. The specification teaches that conditions of "excess vascularization" or "neovascularization" include "a variety of solid tumors such as breast cancer, hemangiomas in infancy, ocular neovascularization associated with diabetes, bleeding disorders of the female reproductive tract, and certain forms of arthritis" (pg 28, lines 10-13). The specification further teaches, "abnormal vascular growth such as occurs in tumors, rheumatoid arthritis, hemiangiomas, angiofibromas, psoriasis and capillary proliferation and diabetes" (pg 2, lines 22-24). The specification also teaches, "a method is further provided for treating abnormal blood vessel formation (hypervascularization) resulting from genetic diseases, chronic degenerative disease, aging, trauma, or infectious agents. Examples include diabetic chronic ulcers, bums, frost bite, ischemic events following stroke and transplantation" (pg 27, lines 26-30). The claims encompass treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. For example, the abnormally enhanced angiogenesis that occurs in ischemia is advantageous for survival of the affected subject rather than harmful. However, the claims lack enablement even with respect to the elected species under consideration (abnormally enhanced vascular growth associated with a solid tumor). Because the claims are not

enabled for this species (for the reasons set forth herein), the enablement of other encompassed species has not been considered.

The specification as originally filed provides minimal guidance to the skilled artisan with respect to practicing the claimed method with any of the envisioned conditions including the elected species (solid tumors). The specification does not provide any *in vivo* working examples of treatment of a condition of "abnormally enhanced vascular growth" with a "Sonic hedgehog blocking antibody". The specification does not provide any *in vitro* models that correlate with *in vivo* treatment.

Examples 3-6 of the specification provide teachings that are very limited in relation to the claimed inventions. Example 3 teaches that exogenous Sonic hedgehog (Shh) protein added to explant culture can "stimulate hematopoiesis in the epiblast mesoderm" in place of visceral mesoderm (pg 44, lines 6-20). Hematopoiesis was assessed by measuring ε-globlin (see description of Figure 9 on pg 8), which the specification teaches as a marker of erythroid cell formation (pg 28, lines 20-21). Example 3 further teaches that Shh or Indian Hedgehog (Ihh) proteins stimulate proliferation adult hematopoietic stem cells isolated from bone marrow and cultured. Example 4 demonstrates that "Shh blocking antibody" reduces ε-globlin expression in cultured murine whole embryo (pg 48). Example 5 demonstrates expression of *patched* and *Gli* (genes that encode hedgehog signaling pathway components) that was "substantially exclusive in the yolk sac mesoderm" (pg 48). Example 6 states that, "both *Indian hedgehog* and *BMP-6* are expressed in early visceral endoderm." Based on these results, the specification asserts that hedgehog proteins "have utility in regulating hematopoiesis and vascular growth in the adult animal" (pg 13, lines 24-25). However, these examples in the specification are all related to *in vitro* hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. As taught in the specification, "[i]n contrast to vascular growth, hematopoiesis is normally a continuous process throughout the life of an adult" (pg 2, lines 26-27). There are no examples related to stimulation or inhibition of vascular growth in either an embryo or an adult in either normal or diseased individuals with a solid tumor.

The post-filing date art does support a role for the hedgehog pathway in the growth and angiogenesis of a certain subset of solid tumors. For example, Nagase et al teaches, "Shh signalling has been implicated in the development of several malignancies including basal cell carcinoma of the skin, lung cancer and medulloblastoma … and it is possible the Shh mediates tumor angiogenesis ... Hh signaling may be enhanced, stimulating tumour angiogenesis" (pg 74 of Nagase et al, 2008. Angiogenesis, 11: 71-77). Yamazaki et al, 2008 teaches (with respect to pancreatic tumors) "[o]ur results imply that SHH secreted from cancer cells facilitates tumor growth not only by stimulating proliferation of cancer in an autocrine manner but also by promoting angiogenesis through EPC activation in a paracrine manner" (pg 1137 of Yamazaki et al, 2008. Cancer Sci. 99(6): 1131-1138). As such, the instant claims encompass inhibition of abnormally enhanced vascular growth associated with a tumor that occurs by (1) directly, by blocking the Shh stimulating paracrine vascular growth; and/or (2) indirectly, by blocking the Shh stimulating autocrine tumor growth, which in turn prevents additional vascular growth associated with the tumor.

However, the post-filing date art makes it clear that many solid tumors do not include dysfunctions that lead to Shh overexpression. For example, Thievessen et al (2005) teaches, "our data suggest that hedgehog pathway is weakly active in normal adult urothelial cells and of limited importance in TCC [transitional cell carcinoma]" (abstract) and "the hedgehog pathway has been reported to become activated in small cell lung cancer, but not in other histological types of lung cancer" (pg 376 of Thievessen et al, 2005. Journal of Cellular Physiology. 203: 372-377; cited previously). Furthermore, even in small cell lung cancer, Watkins et al observed that only 50% of primary tumors (5 of 10) expressed the Sonic hedgehog protein (see page 314 of Watkins et al, 2003. Nature. 422(6929): 313-7 plus 2 pages of Supplementary material; see also Supplementary panel a, the legend for which states "The SCLC case demonsrates [sic] variable co-expression of Shh and Gli1 in tumor cells"). Furthermore, the relevant art teaches that "the published results on primary human colon cancers are also confusing. Some authors, but not others detected increased levels of Hh pathway members during colon cancer progression. Moreover, the expression of Ihh and Gli1

were shown to be decreased during colon cancer progression in recent publications" (see pg 2626 of Chatel et al, 2007. Int J Cancer. 121: 2622-2627; cited previously). Furthermore, U.S. Pre-Grant Application Publication 2004/0110663 (a publication of application 10/652,298; cited on the IDS filed 10/22/07) reports that high levels of *gli-1* expression (as compared with "non-proliferative" cells) are found in some tumors of the prostate, lung, and breast ("8 out of 18 breast cancer samples showed substantially increased gli-1 expression. 7 out of 11 lung cancer samples, 11 of 19 benign prostatic hypertrophy samples (BPH), and 6 out of 15 prostate cancer samples all showed strong gli1 expression"; ¶ 759 of the '663 publication). The '663 publication further reports that the growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by the Sonic hedgehog blocking antibody 5E1 (Figure 54; ¶ 848). Thus, the art provides evidence that many tumors of different tissues do not include activation of the hedgehog signaling pathway such that Shh is overexpressed. This supports the general concept that different conditions of abnormal vascular growth in adult subjects (e.g., solid tumors from different patients) does not necessarily involve expression of the same angiogenic molecules. This variable expression "not only among different tumour types, but also with the same tumour" has also been observed with vascular endothelial growth factor (VEGF), another molecule associated with angiogenesis (pg 394 of Ferrara et al. 2004. Nature Reviews Drug Discover. 5(3): 391-400; cited previously).

Based on limited working examples showing a role of the Sonic hedgehog protein in *in vitro* hematopoiesis, the instant specification asserts that antagonists of Sonic hedgehog signaling, such as a Sonic hedgehog blocking antibody, can be used to treat abnormally enhanced vascular growth, such as the elected species of solid tumor. However, the instant specification contains no recognition that aberrant Shh expression is associated only with certain subset of solid tumors. Instead, the instant specification directs the skilled artisan to treat any solid tumor with a Sonic hedgehog blocking antibody. However, in view of the teachings of the post-filing date art, the skilled artisan would predict that a solid tumor that does not overexpress the Sonic hedgehog protein would fail to be inhibited by administration of a Sonic hedgehog blocking antibody. What is missing from the specification is the critical guidance to first determine that the solid

tumor is associated with misregulation of the Sonic hedgehog signaling pathway that results in Shh overexpression. In view of the lack of guidance provided by the specification and the prior art the skilled artisan could not practice the claimed method without undue experimentation.

Applicants' arguments (6/25/08; pg 7-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants first acknowledge "that the post-filing date art has revealed differing mechanisms by which hedgehog signaling may be misregulated in various types of cancers" including constitutive activation of the hedgehog pathway and overexpression of the hedgehog protein, and modulating each may require different compounds (pg 7-8). Applicants further argue that "the claimed invention is not directed to modulating hedgehog signaling in tumor cells" but rather to "inhibiting enhanced vascular growth" such as that accompanying a solid tumor. Applicants argue that the concept of inhibiting tumor growth by inhibiting the blood supply feeding a tumor is generally accepted in the field of oncology, and is independent of whether the tumor is hedgehog-dependent or -independent. Applicants point to Exhibit 1, which shows a slide from the NCI's website, and to the over 1200 results generated when the NIH clinical trials database is searched with the term angiogenesis, inhibitor and tumor. Applicants further argue that the "specification and post-filing art support a role for hedgehog signaling in vascular growth"; Applicants point to the references Pola (2001) and Pola (2003)(each cited previously) and Applicants' evidence with a Sonic hedgehog blocking antibody. Applicants argue that a working example of using a hedgehog antibody in the context of a tumor is not necessary in view of the pre- and post-filing date art examples of targeting angiogenesis for tumor treatment.

These arguments have been fully considered but are not found to be persuasive. It is maintained that the practicing the claimed methods would require undue experimentation. The Examiner does not dispute that the relevant post-filing date art teaches that hedgehog signaling is involved in some cancers. However, in view of the relevant teachings of the post-filing date art (cited in the rejection above), administration

of a Sonic hedgehog blocking antibody would not result in treatment of a solid tumor unless the tumor exhibits overexpression of the Sonic hedgehog protein. It is acknowledged that determination of the specific mechanism of dysregulation leading to such overexpression is not needed, but determination of such overexpression is necessary to identify those tumors that can be successfully treated with the blocking antibody. It is not disputed that inhibition of angiogenesis is a widely acknowledged strategy in the art for tumor treatment. However, Applicants have provided no evidence that a hedgehog antagonist such as a blocking antibody can inhibit the vascular growth associated of the many solid tumors in which the Sonic hedgehog antibody is not overexpressed. The relevant art provides evidence that tumor-associated angiogenesis is a paracrine effect dependent on secretion of Shh from the tumor (see the teachings of Yamazaki et al, 2008 cited above). There is no evidence in the relevant art that Shh plays a role in tumor angiogenesis independent of tumor expression of Shh. Pola et al (2001) merely provides evidence that the Sonic hedgehog pathway can be become activated in adult cardiovascular tissues; no teaching is provided regarding the predictability of Shh expression in tumors. Pola et al (2003) demonstrates that "skeletal muscle ischemia induces strong local upregulation of Shh mRNA and protein" (see Abstract) and concludes that "the role of Shh as a morphogen may be relevant to its potential activity to orchestrate appropriate postnatal angiogenesis after tissue injury" (pg 484). This teaching suggests that treatment of the abnormally enhanced vascular growth following ischemia (which is envisioned by the specification as part of the claimed invention) with a Shh blocking antibody would be deleterious to recovery from ischemia. Applicants' own evidence with the Sonic hedgehog blocking antibody is limited to working examples regarding *in vitro* hematopoiesis, which is a significantly different process from vascular growth (as discussed in the above rejection).

Applicants further argue that "the second basis of the Examiner's rejection" regarding the "genus of structurally undefined hedgehog signaling antagonists" to be used in the claimed rejection is moot in view of the amendments to the claims that limit the claimed method to a "Sonic hedgehog blocking antibody".

This argument has been fully considered and is found to be persuasive. In view of Applicants' amendments to the claims to limit the antagonist to be used to said antibody, the portion of the rejection directed to the scope of the antagonist to be used in the claimed method is moot.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646